AHCCCS
Arizona Health Care Cost Containment System

AHCCCS Pharmacy and Therapeutics Committee

October 12, 2017

Introductions & Minutes Approval

- Review July 10, 2017 Meeting Minutes
- Amend
- Vote

P&T Membership Update

- For 2018 to 2020

Future P&T Meeting Dates

- **2018 Meeting Dates:**
  - Tuesday, January 16, 2018
  - Tuesday, April 17, 2018
  - Tuesday, July 17, 2018
  - Monday, October 22, 2018-This is a change.

Magellan Class Reviews

Therapeutic Classes

- Hepatitis C Agents
- Cytokine and CAM Antagonists
- Long-Acting Analgesics Narcotics
- Growth Hormones
- Self-Injected Epinephrine
- Inhaled Antibiotics
- Progestational Agents

Magellan Drug Class Reviews

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Hepatitis C Agents

Hepatitis C Agents

Class Overview: Products – Interferons

- peginterferon alfa-2a - (Pegasys ProClick, Syringe & Vials)
- peginterferon alfa-2b - (PegIntron RediPen & Vials)

Class Overview: Products – Ribavirins

- Copegus
- Moderiba
- Rebetol Solution
- Ribasphere & Ribasphere RibaPak
- ribavirin capsules & tablets

Hepatitis C Agents

Class Overview: Products – Direct Acting Agents

- ***Oral Combination Products***
  - elbasvir/grazoprevir – (Zepatier)
  - glecaprevir/pirbrentasvir – (Mavyret)
  - ledipasvir/sofosbuvir – (Harvoni)
  - ombitasvir/paritaprevir/ritonavir/dasabuvir – (Viekira Pak & Viekira XR)
  - ombitasvir/paritaprevir/ritonavir – (Technivie)
  - sofosbuvir/velpatasvir – (Epclusa)
  - sofosbuvir/velpatasvir/voxilaprevir – (Vosevi)

Hepatitis C Agents

Class Overview: Products – Direct Acting Agents

- ***Oral NS5A Inhibitors***
  - daclatasvir – (Daklinza)
- ***Oral NS5B Polymerase Inhibitors***
  - sofosbuvir – (Sovaldi)
- ***Oral Protease Inhibitors***
  - simeprevir – (Olysio)

Hepatitis C Agents

- Currently, the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) Recommendations for Testing, Managing, and Treating Hepatitis C recommends the use of different antiviral therapies based on the genotype identified and co-morbidities
- These clinical parameters help determine appropriate agent selection, likelihood of response, and treatment duration
- The AASLD/IDSA has yet to incorporate the two newest Hepatitis C agents, Mavyret and Vosevi into its guidance
- A guideline update is anticipated in the near future

Hepatitis C Agents

New Product in Class: Mavyret (glecaprevir/pibrentasvir)

- Mavyret is a fixed-dose combination product containing glecaprevir, (a NS3/4A protease inhibitor), and pibrentasvir, (NS5A HCV inhibitor)
- Mavyret is indicated for the treatment of HCV genotypes 1 to 6 in adult patients without cirrhosis or with compensated cirrhosis (Child-Pugh A)
- Mavyret is also indicated in patients who have genotype 1 and have been treated previously with regimens containing either an HCV NS5A inhibitor or an HCV NS3/4A PI, but not both
- Mavyret is approved for a shorter 8-week duration in non-cirrhotic patients who are treatment-naïve or who have failed prior PRS treatment, offering the shortest treatment duration to the broadest eligible patient population

Hepatitis C Agents

New Product in Class: Mavyret (glecaprevir/pibrentasvir)

- Mavyret is contraindicated in patients with severe hepatic impairment (Child-Pugh C)
- Is contraindicated when administered concomitantly with rifampin or atazanavir (Reyataz or Evotaz)
- Carries a boxed warning for the risk of reactivation of hepatitis B virus (HBV) in patients who are infected with both HBV and HCV.
- Patients should be screened for HBV prior to starting therapy and monitored for signs of hepatitis flare or HBV reactivation during treatment and post-treatment follow-up

Hepatitis C Agents

New Product in Class: Mavyret (glecaprevir/pibrentasvir)

- Glecaprevir and pibrentasvir are each inhibitors of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP) 1B1/3
- Glecaprevir and pibrentasvir are also weak inhibitors of cytochrome P450 (CYP) 3A, CYP1A2, and uridine glucuronosyltransferase (UGT) 1A1
- Concomitant use of Mavyret with drugs that are metabolized by P-gp, BCRP, OATP1B1 or OATP1B3 can increase the plasma concentrations of those drugs in the body
- Glecaprevir and pibrentasvir are both substrates of P-gp and/or BCRP transporters and glecaprevir is also a substrate of OATP1B1/3

Hepatitis C Agents

New Product in Class: Mavyret (glecaprevir/pibrentasvir)

- Use of Mavyret with drugs which inhibit or induce P-gp, BRCP, or CYP3A could increase or decrease concentrations of glecaprevir or pibrentasvir, respectively
- Refer to Mavyret prescribing information for a more extensive listing of drugs with potential interactions
- Supplied as tablets containing 100 mg glecaprevir and 40 mg pibrentasvir
- Recommended dosage is three tablets orally once-daily with food
- Treatment duration is dependent on genotype, previous treatments and cirrhosis status

Hepatitis C Agents

New Product in Class: Mavyret (glecaprevir/pibrentasvir)

- Most common adverse reactions (incidence ≥ 10%) in trials were headache and fatigue, diarrhea
- No adequate human data are available to determine whether Mavyret poses a risk in pregnancy
- Safety and efficacy of Mavyret have not been established in patients under 18 years of age
- No dosage adjustment of Mavyret is required in geriatric patients
- No dosage adjustment is recommended in patients with mild hepatic impairment (Child-Pugh A). Mavyret is not recommended with moderate hepatic impairment (Child-Pugh B). It is contraindicated in severe hepatic impairment (Child-Pugh C)

Hepatitis C Agents

New Product in Class: Mavyret (glecaprevir/pibrentasvir)

- No dosage adjustment is required in patients with mild, moderate or severe renal impairment, including dialysis patients
- Efficacy of Mavyret was studied in eight phase 2 and 3 trials in 2,152 subjects diagnosed with HCV genotypes 1 to 6 with or without compensated cirrhosis who were either treatment-naïve or treatment-experienced
- Primary endpoint for each trial was the proportion of patients who achieved a sustained virologic response (SVR), defined as HCV ribonucleic acid (RNA) less than lower limit of quantification (LLOQ) at 12 weeks after stopping study treatment (SVR12)

Hepatitis C Agents

New Product in Class: Mavyret (glecaprevir/pibrentasvir)

- Across all trials, the median age of enrolled patients was 54 years old, 73% were treatment-naïve, 54% were male, 12% had cirrhosis, and 60% were either genotype 1 or 2
- Overall, the SVR12 rate in the Mavyret arms was 97% across all studies
- ENDURANCE-1 was a randomized, open-label, multicenter trial which compared Mavyret 300 mg/120 mg administered daily for 8 weeks versus 12 weeks in patients who were treatment-naïve or treatment-experienced with PRS, but did not have cirrhosis, and were diagnosed with HCV genotype 1 with or without HIV (n=703)

Hepatitis C Agents

New Product in Class: Mavyret (glecaprevir/pibrentasvir)

- The primary endpoint was non-inferiority compared to a historical 91% SVR12 rate established by current approved standard of care regimens (Viekira/XR ± RBV or Harvoni for 12 weeks).
- The results showed that the SVR12 for the 8-week group was 99%, compared to 99.7% in the 12-week group. Both demonstrated non-inferiority to the historical rate, and the 8-week treatment demonstrated non-inferiority to the 12-week treatment
- ENDURANCE-2 was a randomized, double-blind, placebo-controlled, multicenter trial examining the efficacy of Mavyret 300mg/120mg given once daily for 12 weeks in patients with genotype 2 who were non-cirrhotic, treatment-naïve or previously treated with PRS (n-302)

Hepatitis C Agents

New Product in Class: Mavyret (glecaprevir/pibrentasvir)

- The primary endpoint was to test for non-inferiority compared to a 95% historical SVR12 rate of Sovaldi + RBV
- The secondary endpoint was to test for superiority compared to a 95% historical SVR12 rate of Sovaldi + RBV
- The results showed that patients treated with Mavyret for 12 weeks achieved a 99% SVR12, which was both non-inferior and superior to the 95% historical SVR12 rate of Sovaldi + RBV

Hepatitis C Agents

New Product in Class: Mavyret (glecaprevir/pibrentasvir)

- ENDURANCE-3 was a randomized, active-controlled, multicenter trial comparing 8 weeks of Mavyret 300mg/120mg once daily with 12 weeks of Mavyret 300mg/120mg and 12 weeks of Sovaldi 400mg + Daklinza 60mg daily in genotype 3 patients who were treatment-naïve and non-cirrhotic (n=505)
- The primary endpoint was non-inferiority compared to Sovaldi + Daklinza
- The results showed that SVR12 was 95% in both arms of Mavyret, compared to 97% for Sovaldi + Daklinza confirming the 12-weeks treatment was non-inferior to Sovaldi + Daklinza, and the 8-week treatment was non-inferior to the 12-week treatment

Hepatitis C Agents

New Product in Class: Mavyret (glecaprevir/pibrentasvir)

- ENDURANCE-4 was an open-label, multicenter trial measuring the efficacy of Mavyret 300 mg/120 mg daily for 12 weeks in patients with HCV genotypes 4, 5, and 6 who were both treatment-naïve or treatment-experienced with PRS, but did not have cirrhosis (n=121)
- The SVR12 rate was 99% in patients with genotype 4 and 100% in both genotypes 5 and 6

Hepatitis C Agents

New Product in Class: Mavyret (glecaprevir/pibrentasvir)

- EXPEDITION-1 and EXPEDITION-4 were open-label, multicenter trials that measured the efficacy of Mavyret 300 mg/120 mg daily for 12 weeks in patients who were treatment-naïve or treatment-experienced with PRS and with or without cirrhosis (n=250)
- EXPEDITION-1 enrolled patients with HCV genotypes 1, 2, 4, 5, and 6 with HIV.
- EXPEDITION-4 enrolled patients diagnosed with all genotypes who had severe renal impairment or end-stage renal disease (ESRD).
- The SVR12 rate was 99% in EXPEDITION-1 and 98% in EXPEDITION-4
- The incidence of serious adverse events in EXPEDITION-4 was 24%, compared to 11% in EXPEDITION-1

Hepatitis C Agents

New Product in Class: Mavyret (glecaprevir/pibrentasvir)

- EXPEDITION-2 was an open-label, multicenter trial that compared Mavyret 300 mg/120 mg daily for 8 weeks in patients without cirrhosis versus 12 weeks in patients with compensated cirrhosis (n=151)
- Patients enrolled in the study were diagnosed with HCV genotypes 1, 2, 4, 5, or 6 with HIV and could be treatment-naïve or treatment-experienced (IFN/RBV ± Sovaldi)
- The results showed the SVR12 rate was 100% in the patients without cirrhosis who were treated for 8 weeks, 93% for the patients with cirrhosis treated for 12 weeks, and 98% overall

Hepatitis C Agents

New Product in Class: Mavyret (glecaprevir/pibrentasvir)

- MAGELLAN-2 was an open-label, multicenter trial which measured the efficacy of Mavyret 300 mg/120 mg administered daily for 12 weeks in patients with HCV of all genotypes and who were liver or kidney transplant recipients, non-cirrhotic, and were treatment-naïve or treatment-experienced (n=100)
- The primary endpoint was non-inferiority compared to a historical SVR12 rate of 94% established by Harvoni + RBV or Sovaldi + Daklinza + RBV
- The results showed that the SVR12 rate was 98%, which demonstrated non-inferiority to the historical standard of care

Hepatitis C Agents

New Product in Class: Mavyret (glecaprevir/pibrentasvir)

- SURVEYOR-2 Part 3 was an open-label, randomized trial in treatment-naïve and PRS treatment-experienced subjects with genotype 3 infection without cirrhosis to 12- or 16-weeks of treatment
- Non-cirrhotic patients received Mavyret 300 mg/120 mg daily for 12 or 16 weeks
- Patients with compensated cirrhosis were further randomized into two treatment arms, 12-week (treatment-naïve only) and 16-week (PRS treatment-experienced only)
- SVR12 rate was 95%, 98%, and 96% in the non-cirrhotic, treatment-naïve with compensated cirrhosis, and treatment experienced with com compensated cirrhosis arm, respectively

Hepatitis C Agents

New Product in Class: Vosevi (sofosbuvir/velpatasvir/voxilaprevir)

- Vosevi is a fixed-dose combination product containing sofosbuvir, (a NS5B polymerase inhibitor), velpatasvir, (a NS5A HCV inhibitor), and voxilaprevir, (a NS3/4A protease inhibitor)
- Vosevi is indicated for the treatment of chronic HCV infection in patients without cirrhosis or with compensated cirrhosis (Child-Pugh A) with genotype 1-6 infections, previously treated with an NS5A inhibitor; or genotype 1a or 3 infections previously treated with sofosbuvir without an NS5A inhibitor
- Additional benefit of Vosevi over Epclusa was not shown in adults with genotype 1b, 2, 4, 5, or 6 infections previously treated with sofosbuvir without an NS5A inhibitor
- Vosevi is the first product approved by the FDA for patients who failed prior DAA therapy

Hepatitis C Agents

New Product in Class: Vosevi (sofosbuvir/velpatasvir/voxilaprevir)

- Is contraindicated when administered concomitantly with rifampin
- Carries a boxed warning for the risk of reactivation of hepatitis B virus (HBV) in patients who are infected with both HBV and HCV.
- Patients should be screened for HBV prior to starting therapy and monitored for signs of hepatitis flare or HBV reactivation during treatment and post-treatment follow-up
- Symptomatic bradycardia has been reported in patients who received concomitant therapy with a sofosbuvir-containing regimen and amiodarone. Bradycardia has generally occurred within hours or days, but could take as long as 2 weeks after starting treatment

Hepatitis C Agents

New Product in Class: Vosevi (sofosbuvir/velpatasvir/voxilaprevir)

- Sofosbuvir, velpatasvir, and voxilaprevir are substrates of P-glycoprotein (P-gp) and BCRP transporters. Voxilaprevir is also a substrate of OATP1B1/3 (organic anion transport polypeptide). Changes to the metabolism of velpatasvir caused by CYP2B6, CYP2C8, and CYP3A4; and of voxilaprevir by CYP1A2, CYP2C8, and primarily CYP3A4, have been observed in vitro
- Known inducers of P-gp, and moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 could decrease sofosbuvir, velpatasvir, and/or voxilaprevir levels, reducing efficacy. These drugs are not recommended to be used with Vosevi. Vosevi can be used with P-gp, BCRP, and CYP inhibitors; however, use with OATP inhibitors that increase voxilaprevir exposure is not recommended

Hepatitis C Agents

New Product in Class: Vosevi (sofosbuvir/velpatasvir/voxilaprevir)

- Velpatasvir and voxilaprevir are known inhibitors of P-gp, BCRP, and OATP1B1/3, and velpatasvir inhibits OATP2B1. The use of Vosevi concomitantly with drugs that are metabolized by these transporters may alter drug concentrations of those drugs in vivo. Use of Vosevi with drugs metabolized by BCRP is not recommended
- Refer to Vosevi prescribing information for a more extensive listing of drugs with potential interactions
- Supplied as tablets containing 400 mg sofosbuvir, 100 mg velpatasvir, and 100 mg voxilaprevir
- Recommended dosage is one tablet orally once-daily with food for 12 weeks

Hepatitis C Agents

New Product in Class: Vosevi (sofosbuvir/velpatasvir/voxilaprevir)

- Most common adverse reactions (incidence ≥ 10%) in trials were headache, fatigue, diarrhea, and nausea
- No adequate human data are available to determine whether Vosevi poses a risk in pregnancy
- Safety and efficacy of Vosevi have not been established in pediatric patients
- No dosage adjustment of Vosevi is required in geriatric patients
- No dosage adjustment is recommended in patients with mild hepatic impairment (Child-Pugh A). Vosevi is not recommended with moderate or severe hepatic impairment (Child-Pugh B or C)

Hepatitis C Agents

New Product in Class: Vosevi (sofosbuvir/velpatasvir/voxilaprevir)

- No dosage adjustment is recommended in patients with mild or moderate renal impairment
- Safety and efficacy for Vosevi have not been established in patients with severe renal impairment
- Efficacy of Vosevi was studied in two placebo-controlled trials (POLARIS-1 and POLARIS-4) in 748 patients.
- POLARIS-1 included patients diagnosed with HCV genotypes 1 to 6, with or without compensated cirrhosis, who failed a regimen containing NS5A inhibitors. POLARIS-4 included patients with genotype 1, 2, 3, or 4, with or without compensated cirrhosis, who failed a DAA-containing regimen that did not include an NS5A inhibitor

Hepatitis C Agents

New Product in Class: Vosevi (sofosbuvir/velpatasvir/voxilaprevir)

- Both trials were 12 weeks in duration. In POLARIS-1, patients were blinded and randomized to receive Vosevi or placebo. In POLARIS-4, patients were randomized open-label to receive Vosevi or Epclusa. All doses were administered once-daily by mouth in these trials
- The primary endpoint for both trials was the proportion of patients who achieved a sustained virologic response (SVR), defined as HCV RNA less than lower limit of quantification (LLOQ) at 12 weeks after stopping study treatment (SVR12). In POLARIS-1, the Vosevi group achieved an overall SVR12 of 96%, compared to 0% in the placebo group ($p<0.001$)
- In POLARIS-4, the Vosevi arm achieved an overall SVR12 rate of 97%, compared to 88% in the Epclusa arm ($p<0.001$)

Hepatitis C Agents

New Product in Class: Vosevi (sofosbuvir/velpatasvir/voxilaprevir)

- In genotypes 1a and 3, the SVR12 rate was 97% and 96% for the Vosevi arm compared to 82% and 85% for the Epclusa arm
- In POLARIS-4, Vosevi was administered for 12 weeks to 18 HCV genotype 4 subjects, with or without cirrhosis who had prior exposure to a sofosbuvir-containing regimen without an NS5A inhibitor. All subjects achieved SVR12

Hepatitis C Agents

Product Updates:

- A boxed warning has been added to all direct-acting antivirals in this class due to the potential for reactivating hepatitis B virus (HBV). In addition, information regarding testing for evidence of current or prior HBV infection has been added to Dosage & Administration
- Technivie is now indicated for treatment of chronic hepatitis C genotype 4 with compensated cirrhosis; previously only approved in genotype 4 patients without cirrhosis
- Sovaldi (in combination with ribavirin) is now indicated for the treatment of HCV genotypes 2 or 3 in children 12 years of age and older weighing 35 kg or greater without cirrhosis or with mild cirrhosis

Hepatitis C Agents

Product Updates:

- Harvoni is now indicated for the treatment of HCV genotypes 1,4,5 or 6 in children 12 years of age and older weighing 35 kg or greater without cirrhosis or with mild cirrhosis
- Epclusa is now indicated for the treatment of chronic HCV (genotypes 1-6) in patients who are HCV/HIV co-infected. No change in dosage is needed with HIV co-infection

Hepatitis C Agents

Guideline Updates:

- The AASLD/IDSA hepatitis C treatment guidelines have been updated. Key updates include a new initial therapy recommendation to shorten the duration of Harvoni in patients without cirrhosis to 8 weeks for non-black, HIV-uninfected patients with HCV RNA is < 6 million IU/mL when used for initial treatment, updated grading of Epclusa for genotype 5 and 6 infections, and updated recommendations for retreatment of genotype 3 infection
- *Global changes throughout guidance; resistance-associated variants (RAV) terminology has been changed to resistance-associated substitutions (RAS) and the standardized renal function parameter has changed from creatinine clearance (CrCl) to estimated glomerular filtration rate (eGFR)*

Cytokine and CAM Antagonists

Cytokine and CAM Antagonists

Class Overview: Products – TNF Agents

- adalimumab - (Humira Kit & Pen Kit)
- certolizumab pegol - (Cimzia Kit & Syringe Kit)
- etanercept - (Enbrel Kit, Pen & Syringe)
- golimumab SC - (Simponi Pen Injector & Syringe)
- golimumab IV - (Simponi Aria Vials)
- infliximab - (Remicade Vials)

Cytokine and CAM Antagonists

Class Overview: Products – Non-TNF Biologic Agents

- abatacept - (Orencia ClickJet, Syringe & Vials)
- anakinra - (Kineret Syringe)
- brodalumab - (Siliq Syringe)
- canakinumab - (Ilaris Vials)
- guselkumab - (Tremfya Syringe)
- ixekizumab - (Taltz AutoInjector & Syringe)
- rilonacept - (Arcalyst Vials)
- sarilumab - (Kevzara Syringe)
- secukinumab- (Cosentyx Pen & Syringe)

Cytokine and CAM Antagonists

Class Overview: Products – Non-TNF Biologic Agents

- tocilizumab - (Actemra Syringe & Vials)
- ustekinumab - (Stelara Syringe & Vials)
- vedolizumab - (Entyvio Vials)

Class Overview: Products – Non-Biologic Agents

- apremilast (Otezla Tablets)
- tofacitinib (Xeljanz, Xeljanz XR Tablets)

Cytokine and CAM Antagonists

Drug	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Ankylosing Spondylitis	Plaque Psoriasis	Psoriatic Arthritis	Crohn's Disease	Ulcerative Colitis
TNF Agents							
adalimumab (Humira®)	X	X (≥ 2 years)	X	X	X	X (≥ 6 years)	X
certolizumab pegol (Cimzia®)	X	--	X	--	X	X	--
etanercept (Enbrel®)	X	X (≥ 2 years)	X	X (≥ 4 years)	X	--	--
golimumab SC (Simponi®)	X	--	X	--	X	--	X
golimumab IV (Simponi® Aria®)	X	--	--	--	--	--	--
infliximab (Remicade®)	X	--	X	X	X	X (≥ 6 years)	X (≥ 6 years)

Cytokine and CAM Antagonists

Drug	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Ankylosing Spondylitis	Plaque Psoriasis	Psoriatic Arthritis	Crohn's Disease	Ulcerative Colitis
Other Biologic Agents							
abatacept (Orencia®)	X	X (≥ 6 years: IV) (≥ 2 years: SC)	--	--	X	--	--
anakinra (Kineret®)	X	--	--	--	--	--	--
brodalumab (Siliq™)	--	--	--	X	--	--	--
canakinumab (Ilaris®)	--	X (≥ 2 years)	--	--	--	--	--
guselkumab (Tremfya™)	--	--	--	X	--	--	--
ixekizumab (Taltz®)	--	--	--	X	--	--	--

Cytokine and CAM Antagonists

Drug	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Ankylosing Spondylitis	Plaque Psoriasis	Psoriatic Arthritis	Crohn's Disease	Ulcerative Colitis
Other Biologic Agents							
rilonacept (Arcalyst®)	--	--	--	--	--	--	--
sarilumab (Kevzara®)	X	--	--	--	--	--	--
secukinumab (Cosentyx®)	--	--	X	X	X	--	--
tocilizumab (Actemra®)	X	X (≥ 2 years) (IV only)	--	--	--	--	--
ustekinumab (Stelara®)	--	--	--	X	X	X	--
vedolizumab (Entyvio®)	--	--	--	--	--	X	X

Cytokine and CAM Antagonists

Drug	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Ankylosing Spondylitis	Plaque Psoriasis	Psoriatic Arthritis	Crohn's Disease	Ulcerative Colitis
Non-Biologic Agents							
apremilast (Otezla®)	--	--	--	X	X	--	--
tofacitinib (Xeljanz®, Xeljanz XR®)	X	--	--	--	--	--	--

Cytokine and CAM Antagonists

- Cytokines and CAMs have indications for use in rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, Crohn's disease, ankylosing spondylitis as well as other disease states
- For many disease states, including rheumatoid arthritis there is no evidence that any one TNF antagonist should be used before another.
- There is no evidence that any one TNF antagonist is more effective than any other for the treatment of RA or AS
- In the absence of specific head-to-head trials there is no indication of a specific 'first choice' for treatment in many of the targeted diseases so secondary indicators such as adverse reactions and cost may be considered
- Many of the guideline documents do not include some of the newer agents

Cytokine and CAM Antagonists

New Product in Class: Siliq (brodalumab)

- Siliq is a human interleukin-17 receptor A (IL-17RA) antagonist indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy
- Siliq is the third approved IL-17A inhibitor (Cosentyx & Taltz are others)
- Contraindicated in patients with Crohn's disease as it may worsen the disease. Discontinue if Crohn's disease develops during treatment
- Carries a boxed warning regarding suicidal ideation and behavior. Prescribers should weigh the risk and benefits when prescribing brodalumab to patients with a history of depression or suicidality

Cytokine and CAM Antagonists

New Product in Class: Siliq (brodalumab)

- Due to the observed suicidal ideation and behavior, if adequate response in not seen within 12 to 16 weeks, discontinuation of therapy should be considered
- Siliq is only available through a REMS Program due to the observed suicidal ideation and behavior in patients treated
- Warnings include serious infections, tuberculosis, and exacerbations of inflammatory bowel diseases
- Live vaccines should not be administered with Siliq
- Common adverse reactions include arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection site reactions and influenza

Cytokine and CAM Antagonists

New Product in Class: Siliq (brodalumab)

- There are no human data in pregnant women to make an informed a drug-associated risk assessment
- Starting recommended dose is 20mg subcutaneously at weeks 0, 1 and 2 followed by every two weeks afterwards
- Supplied as 201mg per 1.5ml solution

Cytokine and CAM Antagonists

New Product in Class: Siliq (brodalumab)

- Safety and efficacy was evaluated in three multicenter, randomized, double-blind, controlled trials (AMAGINE-1,-2, and-3) of 4,373 adult patients with moderate to severe plaque psoriasis for at least six months and eligible for phototherapy. Patients were required to have a minimum affected body surface area (BSA) of 10%, a Psoriasis Area and Severity Index (PASI) score that was ≥ 12, and a static Physician's Global Assessment (sPGA) score of ≥ 3 in overall assessment (e.g., erythema, plaque thickness/induration, scaling) of psoriasis on a 0 to 5 severity scale

Cytokine and CAM Antagonists

New Product in Class: Siliq (brodalumab)

- Study patients were randomized to subcutaneous placebo or brodalumab 210 mg at Weeks 0, 1, and 2 and every 2 weeks thereafter for 12 weeks.
- AMAGINE-2 and -3 trials were active comparator trials that included an ustekinumab group dosed as either 45 mg or 90 mg (weight based) at Weeks 0, 4, and 16 followed by the same dose every 12 weeks.
- The trials had two co-primary endpoints from baseline to Week 12: proportion of patients achieving PSI 75 and proportion of patients with a sPGA of 0 or 1 (clear or almost clear, respectively) and ≥ 2 point improvement from baseline

Cytokine and CAM Antagonists

New Product in Class: Siliq (brodalumab)

- At Week 52, percent of patients with improved sPGA of 0 and PASI scores was greater in the Siliq arm for the AMAGINE-1,-2,-3 trials
- The authors concluded brodalumab therapy provided significant improvements for patients with moderate to severe psoriasis
- The trials were funded by Amgen

Cytokine and CAM Antagonists

New Product in Class: Tremfya (guselkumab)

- Tremfya is a human interleukin-23 receptor (IL-23) antagonist indicated for the treatment of moderate to severe plaque psoriasis in patients eighteen years and older who are candidates for systemic therapy or phototherapy
- Tremfya is the first approved IL-23 inhibitor
- There are no known contraindications to Tremfya
- Patients should be evaluated for tuberculosis (TB) infection prior to starting therapy. Treatment for latent TB should be started prior to Tremfya therapy
- Patients should be current on all age appropriate immunizations prior to starting therapy and live vaccines should be avoided when using Tremfya

Cytokine and CAM Antagonists

New Product in Class: Tremfya (guselkumab)

- Tremfya can increase the risk of infections including upper respiratory tract infections, gastroenteritis, ear infections, and herpes simplex infections
- Live vaccines should not be administered with Tremfya
- Commonly reported (≥ 1%) adverse reactions in included upper respiratory infections, headache, injection site reactions, arthralgia, diarrhea, gastroenteritis, tinea infections, and herpes simplex infections
- There is no available data in pregnant women to make an informed a drug-associated risk assessment
- Safety and efficacy has not been established in pediatrics

Cytokine and CAM Antagonists

New Product in Class: Tremfya (guselkumab)

- Tremfya is administered as a 100 mg SC injection at weeks 0 and 4 and every 8 weeks thereafter
- Tremfya is supplied as 100mg/mL pre-filled syringes
- VOYAGE-1 trial was a phase 3, double-blind, placebo- and active-comparator trial, conducted to assess the efficacy and safety of Tremfya compared to Humira in patients ≥ 18 years old for treatment of moderate to severe plaque psoriasis
- Patients were randomized to Tremfya 100 mg (weeks 0 and 4, then every 8 weeks; n=329); placebo then Tremfya (placebo at weeks 0, 4, and 12, then Tremfya weeks 16 and 20 and every 8 weeks thereafter; n=174); or Humira (80 mg week 0, 40 mg week 1, then 40 mg every 2 weeks through week 47; n=334)

Cytokine and CAM Antagonists

New Product in Class: Tremfya (guselkumab)

- Tremfya was superior ($p<0.001$) to placebo and Humira at week 16, 24 and 48 using PASI scores
- VOYAGE 2 trial was a phase 3, multicenter, randomized, double-blind, placebo and Humira comparator-controlled study to assess efficacy and safety of Tremfya in adults with moderate to severe psoriasis
- The study included interrupted treatment and changing Humira non-responders to Tremfya
- At week 16, a greater proportion of patients achieved an IGA 0/1, PASI 90, and PASI 75 response when treated with Tremfya compared to Humira
- Rates continued for 24 weeks and 48 weeks

Cytokine and CAM Antagonists

New Product in Class: Tremfya (guselkumab)

- NAVIGATE trial evaluated the efficacy and safety of Tremfya in patients with moderate to severe plaque psoriasis who have an inadequate response to Stelara
- The study was a randomized, double-blind study with 871 participants receiving Stelara (45 mg or 90 mg; open-label) at weeks 0 and 4. At week 16, patients with an inadequate response to Stelara were randomized (double-blind) to Tremfya 100 mg or to continue using Stelara (67% of patients with IGA 0/1 at week 16 continued open-label Stelara)
- At week 28 and week 52, a greater proportion of Tremfya patients achieved IGA 0/1 and ≥ 2 grade improvement compared to the randomized Stelara patients

Cytokine and CAM Antagonists

New Product in Class: Tremfya (guselkumab)

- A greater proportion of Tremfya treated patients achieved a PASI 90 (51.1% versus 24.1%, respectively; $p<0.001$)
- All three trials were funded by Janssen

Cytokine and CAM Antagonists

New Product in Class: Kevzara (sarilumab)

- Kevzara is an interleukin-6 receptor A (IL-6) antagonist indicated for treatment of moderate to severely active rheumatoid arthritis who have had an inadequate response/intolerance to one or more DMARDs
- Kevzara is the second approved IL-17A inhibitor (Actemra is the other)
- Warnings include serious infections, tuberculosis, invasive fungal infections as well as other opportunistic infections
- Patients may experience reactivation of herpes zoster and concurrent use with biological DMARDs should be avoided
- Treatment may lead to higher incidences of neutropenia, thrombocytopenia, and elevated liver enzymes; laboratory values should be evaluated prior to therapy, at 4 and 8 weeks after starting therapy, and every 3 months after

Cytokine and CAM Antagonists

New Product in Class: Kevzara (sarilumab)

- Lipid abnormalities have been associated with Kevzara and levels should be assessed 4 to 8 weeks after starting therapy, then every 6 months.
- Gastrointestinal perforations have been associated with use of Kevzara.
- Risk may be increased with concurrent diverticulitis or concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids.
- Treatment with immunosuppressants, such as Kevzara, may increase the risk of malignancies

Cytokine and CAM Antagonists

New Product in Class: Kevzara (sarilumab)

- Caution should be taken with concurrent use of Kevzara and CYP3A4 substrates that may lead to a loss of efficacy. This effect may continue for several weeks after discontinuing Kevzara therapy
- Live vaccines should be avoided in patients taking Kevzara
- Most common adverse reactions (incidence at least 3%) reported in clinical trials were neutropenia, increased alanine aminotransferase (ALT), injection site erythema, upper respiratory tract infections, and urinary tract infections
- There is limited data on use in pregnant women to make an informed a drug-associated risk assessment
- Safety and efficacy in pediatrics has not been established

Cytokine and CAM Antagonists

New Product in Class: Kevzara (sarilumab)

- The recommended dose is 200 mg once every 2 weeks administered as a subcutaneous (SC) injection
- Safety and efficacy was evaluated in two pivotal randomized, double-blind, placebo-controlled trials in adult patients with moderately to severely active RA
- In Study 1, patients (n=1,197) with inadequate response to MTX received Kevzara 150 mg or 200 mg or placebo administered SC every 2 weeks in addition to MTX.
- In Study 2, patients (n=546) with inadequate response to at least 1 TNFα inhibitor were randomized to Kevzara 150 mg, Kevzara 200 mg, or placebo administered SC every 2 weeks with concurrent conventional DMARD

Cytokine and CAM Antagonists

New Product in Class: Kevzara (sarilumab)

- The primary endpoint in both trials was the proportion of patients who achieved ACR20 at week 24
- A significantly greater proportion of patients that received Kevzara 150 mg and 200 mg achieved ACR20 compared to those who received placebo at week 24 (Study 1: 58% and 66.4% versus 33.4%, respectively; Study 2: 55.8% and 60.9% versus 33.7%, respectively)
- Similar proportions were seen at week 12 in both studies
- The MONARCH trial was a randomized, active-controlled, double-blind, double-dummy, phase 3 superiority trial comparing monotherapy with Kevzara (200 mg every 2 weeks) and Humira (40 mg every 2 weeks) in 369 patients with RA who had an inadequate response or were intolerant to MTX

Cytokine and CAM Antagonists

New Product in Class: Kevzara (sarilumab)

- After week 16, dose escalation of Humira was allowed in patients who did not achieve 20% improvement in tender and swollen joint counts
- The primary endpoint was Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR) at week 24
- Kevzara was found to be superior as defined by at least 0.6 units improvement over adalimumab using a standard deviation of 1.7
- Rates of injection site reactions reported were higher for sarilumab as well as a higher incidence of neutropenia than adalimumab while the incidence of infection was similar
- Supplied as pre-filled syringes of 150mg/1.14ml or 200mg/1.14ml

Cytokine and CAM Antagonists

New Products/Product Updates:

- Ilaris is now indicated for Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD), and familial Mediterranean fever (FMF) (previously indicated for cryopyrin-associated periodic syndromes (CAPS) and active systemic juvenile idiopathic arthritis)
- Stelara is now indicated for treatment of adults with moderate-to-severe Crohn's disease who have failed or were intolerant to immunomodulators or corticosteroids, but never failed or were intolerant to a TNF inhibitor (previously approved for treatment of moderate-to-severe plaque psoriasis and active psoriatic arthritis)

Cytokine and CAM Antagonists

New Products/Product Updates:

- Enbrel is now indicated for the treatment of plaque psoriasis in patients four to 17 years old (previously indicated only for adults with this indication)
- Ilaris will be available as a 150 mg/mL solution in single-dose vials, eliminating the need for reconstitution. The lyophilized formulation will be discontinued over time
- Orencia is now indicated for moderate to severe active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older, as monotherapy or concomitantly with methotrexate, (previously only for patients 6 years of age and older). Two new strengths are approved for the new age group with weight-based dosing (50mg/0.4mL, 87.5 mg/0.7mL)

Cytokine and CAM Antagonists

New Products/Product Updates:

- Actemra is now approved for giant cell arthritis (GCA) in adults. The recommended dose is 162 mg once every week as a subcutaneous injection, in combination with a tapering course of corticosteroids
- Orencia is now approved for adult psoriatic arthritis
- Actemra I.V. is now approved for patients greater or equal to 2 years of age with chimeric antigen receptor (CAR)-T cell-induced severe or life-threatening cytokine release syndrome (CRS). For this Actemra is dosed as 8 or 12 mg/kg (based on body weight; maximum of 800 mg/infusion) IV as a 60 minute infusion along or in combination with corticosteroids. Additional doses, up to three, may be used if needed

Cytokine and CAM Antagonists

Recent Studies:

- The EXXELERATE study was a comparison of the addition of Cimzia or Humira in patients with rheumatoid arthritis who had failed methotrexate alone
- Primary endpoint was for superiority of Cimzia, which was not met
- The study funding was provided by UCB

Cytokine and CAM Antagonists

Guideline Update:

- There were no appreciable guideline updates since the last class review

Analgesics, Long-Acting Opioids

Analgesics, Long Acting Opioids

Class Overview: Products

- buprenorphine (buprenorphine transdermal, Butrans)
- buprenorphine HCl (Belbuca)
- fentanyl (Duragesic Matrix, fentanyl transdermal)
- hydrocodone bitartrate (Hysingla ER, Vantrela ER & Zohydro ER)
- hydromorphone HCl (Exalgo, hydromorphone ER)
- methadone HCl (methadone concentrate, solution, tablet & sol tab)
- morphine sulfate (Arymo ER, Kadian, Morphabond ER, morphine ER capsule (gen. Avinza & Kadian), morphine ER tablet, MS Contin)

Analgesics, Long Acting Opioids

Class Overview: Products

- morphine sulfate/naltrexone (Embeda)
- oxycodone HCl (oxycodone ER, Oxycontin)
- oxycodone myristate (Xtampza ER)
- oxymorphone HCl (*Opana ER*,* oxymorphone ER)
- tapentadol HCl (Nucynta ER)
- tramadol HCl (Conzip, tramadol ER (gen. Conzip, Ryzolt & Ultram))

- **Voluntarily withdrawn from the market in 2017*

Analgesics, Long Acting Opioids

Abuse -Deterrent Products:

- hydrocodone (Hysingla ER)*
- morphine sulfate (Arymo ER & Morphabond)*
- morphine sulfate/naltrexone (Embeda)*
- oxycodone (OxyContin, oxycodone ER (gen. for OxyContin) & Xtampza ER)*

*These products have met FDA requirements to be approved as abuse-deterrent formulations

Analgesics, Long Acting Opioids

Abuse -Deterrent Products: continued

- hydrocodone ER (Vantrela ER, Zohydro ER)**
- hydromorphone ER (Exalgo)**
- oxymorphone ER (*Opana ER****)**
- tapentadol ER (Nucynta ER)**

**These products have abuse-deterrent properties but have not been approved by the FDA as abuse-deterrent

****Voluntarily withdrawn from the market in 2017*

Analgesics, Long Acting Opioids

- Opioid agonists reduce pain through interaction with opioid mu-receptors located in the brain, spinal cord, and smooth muscle
- The primary site of therapeutic action is the central nervous system (CNS)
- Opioid agonists produce respiratory depression by direct action on the brain stem respiratory center
- Buprenorphine is a partial agonist/antagonist of opioid receptors

Analgesics, Long Acting Opioids

- No clinical data exist that distinguish analgesic efficacy of any of these products from the others
- Abuse deterrent formulations do not enhance analgesic properties
- Pain management must be individualized and patients who do not respond to one opioid may respond to another
- All opioids can be abused and are subject to illicit use
- Abuse deterrent formulations are intended to make misuse more difficult, but do not affect diversion

Analgesics, Long Acting Opioids

- ***New Product in Class: Arymo ER (morphine sulfate)***
- Extended-release opioid agonist with abuse-deterrent properties (polymer matrix with physical and chemical barriers)
- Arymo ER does not use the opioid antagonist naloxone in its formulation
- Approved for management of pain in adults severe enough to require around-the-clock long-term opioid treatment
- Not indicated for as needed analgesia and reserved for patients without treatment alternatives to opioids
- Warnings and precautions are consistent and similar to those experienced with other opioid analgesics including boxed warnings for addiction and misuse

Analgesics, Long Acting Opioids

New Product in Class: Arymo ER (morphine sulfate)

- Recommended starting dose is 15mg given orally every 8 to 12 hours; tablets are to be swallowed whole with plenty of water
- Use in pregnant women may result in neonatal opioid withdrawal syndrome but there is no clear association with use of morphine and major birth defects
- Common adverse events impactful drug interactions are consistent and similar to those experienced with other extended release morphine opioid analgesics
- Safety and efficacy for Arymo ER was approved using 505(b)(2) pathway data based on clinical trials from MS Contin. Clinical trials for efficacy are not included in the drug labeling

Analgesics, Long Acting Opioids

New Product in Class: Arymo ER (morphine sulfate)

- Product is available as 15mg, 30mg and 60mg extended-release tablets
- Arymo ER was added to the Risk Evaluation and Mitigation Strategies (REMS) for long-acting opioids
- Arymo ER has abuse-deterrent properties that increase resistance to cutting, crushing, or grinding the tablet; when in contact with the liquid, it becomes a viscous hydrogel to deter from injectable abuse
- There are no comparative data available

Analgesics, Long Acting Opioids

New Product in Class: Vantrela ER (hydrocodone bitartrate)

- Extended-release opioid agonist and while not part of its labeling, appears to utilize CIMA Labs proprietary abuse-deterrent properties (polymer matrix with excipients)
- Approved for management of pain in adults severe enough to require around-the-clock long-term opioid treatment
- Not indicated for as needed analgesia and reserved for patients without treatment alternatives to opioids
- Warnings and precautions are consistent and similar to those experienced with other opioid analgesics including boxed warnings for addiction and misuse

Analgesics, Long Acting Opioids

New Product in Class: Vantrela ER (hydrocodone bitartrate)

- Recommended starting dose is 15mg given orally every 12 hours; tablets are to be swallowed whole with a maximum dose of 90mg every 12 hours
- There is no available data on the use of Vantrela ER in pregnant women to provide information on drug associated risks
- Common adverse events impactful drug interactions are consistent and similar to those experienced with other hydrocodone opioid analgesics

Analgesics, Long Acting Opioids

New Product in Class: Vantrela ER (hydrocodone bitartrate)

- Safety and efficacy for Vantrela ER was demonstrated in a multicenter, randomized, double-blind placebo-controlled clinical trial involving 625 opioid-naïve and opioid-experienced patients.
- In a six week open-label phase patients were titrated to a successful analgesic dose without exceeding the allowed total daily dose.
- Afterwards, patients were randomized one-to-one to placebo or active therapy with a tapering schedule for the twelve week design period. The proportion of patients experiencing at least a thirty percent reduction in worst pain intensity was greater in the treatment arm than the placebo arm.

Analgesics, Long Acting Opioids

New Product in Class: Vantrela ER (hydrocodone bitartrate)

- Product is available as 15mg, 30mg, 45mg, 60mg and 90mg extended-release tablets
- The American Pain Society guidelines have not been updated since 2009 and do not address most abuse deterrent formulations

Analgesics, Long Acting Opioids

Product Updates:

- The FDA requires abuse-deterrence studies be conducted for approval as such a product, not just the addition of an abuse-deterrent property
- The FDA requested Endo Pharmaceuticals remove reformulated Opana ER from the market based on a postmarketing review which demonstrated a significant shift in the abuse of Opana ER from nasal to injection following reformulation of the product - Endo voluntarily removed Opana ER from the market
- Butrans is now available as a generic

Analgesics, Long Acting Opioids

Guideline/Regulatory Updates: continued

- In an updated guidance, the American College of Physicians (ACP) recommend nonpharmacological therapy (e.g., heat, massage) as first line treatment of acute/subacute low back pain lasting 12 weeks or less
- NSAIDs or skeletal muscle relaxants may be used; acetaminophen is no longer recommended. For chronic pain, first-line therapy is also nonpharmacological. NSAIDs may be added if needed, then tramadol or duloxetine.
- Only consider opioids if prior therapy fails and potential benefits outweigh risks

Analgesics, Long Acting Opioids

Guideline/Regulatory Updates: continued

- American Society of Interventional Pain Physicians (ASIPP) updated their opioid prescribing guidelines for management of chronic, non-cancer pain.
- Methadone is recommended only after failure of another opioid, long-acting opioids should be avoided during initiation, long-acting or high dose opioids should only be used in special circumstances.
- Similar effectiveness for long-acting and short-acting opioids, but greater risk with long-acting opioids

Analgesics, Long Acting Opioids

Guideline/Regulatory Updates: continued

- FDA issued a Safety Communication restricting the use of codeine and tramadol medications in children due to the increased risk of slowed or difficult breathing and death in patients less than 12 years of age
- Single-ingredient codeine and all tramadol-containing products are approved for adults only
- Contraindications regarding use of codeine for pain/cough and tramadol for pain in patients less than 12 years of age, and tramadol for the treatment of pain after tonsillectomy or adenoidectomy in patients less than 18 years of age have been added to product labeling

Analgesics, Long Acting Opioids

Guideline/Regulatory Updates: continued

- The Institute for Clinical and Economic Review (ICER) has published a final report on abuse-deterrent formulation (ADF) opioids. They voted that evidence is adequate to suggest a reduced risk of abuse among patients prescribed OxyContin compared to non-ADF opioids
- Evidence is not sufficient to show a reduced risk of abuse for patients being prescribed any other abuse-deterrent ER opioid assessed in the report (Embeda, Targiniq ER, Hysingla ER, MorphaBond, Xtampza ER, Troxyca ER, Arymo ER, Vantrela ER

Analgesics, Long Acting Opioids

Guideline/Regulatory Updates: continued

- The American Association of Oral & Maxillofacial Surgeons (AAOMS) issued a White Paper regarding opioid prescribing for acute and postoperative pain management
- NSAIDs are recommended over opioids as first-line therapy to manage acute and post-operative pain
- If an opioid is needed, the lowest dose for the shortest duration should be used and ER formulations avoided

Growth Hormones

Growth Hormones

Class Overview: Products

- Genotropin cartridge & syringe (somatropin)
- Humatrope cartridge & vial (somatropin)
- Norditropin pens (somatropin)
- Nutropin AQ NuSpin cartridge (somatropin)
- Omnitrope cartridge & vial (somatropin)
- Saizen cartridge & vials (somatropin)
- Serostim vials (somatropin)
- Zomacton vials (somatropin)
- Zorbtive vials (somatropin)

Growth Hormones

- The primary indication for these products is growth hormone deficiency (GHD): Genotropin; Humatrope; Norditropin; Nutropin AQ; Omnitrope; Saizen and Zomacton (pediatric only) carry this indication
- Several products carry an indication for Turner Syndrome: Genotropin; Humatrope; Norditropin; Nutropin AQ; Omnitrope
- Four products are indicated for Idiopathic Short Stature: Genotropin; Humatrope; Nutropin AQ; Omnitrope
- Four products are indicated for Small for Gestational Age: Genotropin; Humatrope; Norditropin; Omnitrope

Growth Hormones

- Genotropin and Omnitrope are indicated for Prader-Willi Syndrome
- Humatrope is also indicated for Short Stature Homeobox Gene
- Serostim is indicated for HIV wasting or cachexia to increase lean body mass only
- Zorbtive is indicated for Short Bowel Syndrome only

Growth Hormones

- Growth hormone replacement products are, by definition, similar in their clinical effects
- No head-to-head data are available
- No pharmacologic difference among the agents exists in terms of safety and efficacy
- The 2009 American Association of Clinical Endocrinologists Clinical Practice Guidelines indicated no evidence to support any specific product over another

Growth Hormones

Product/Guideline Updates:

- There is no recent clinical information or product specific news of significance for this class

Epinephrine, Self-injected

Epinephrine, Self-Injected

Class Overview: Products

- *Auvi-Q (epinephrine)**
- epinephrine 0.15mg & 0.3mg [gen. Epi-Pen] (epinephrine)
- epinephrine 0.15mg & 0.3mg [gen. Adrenaclick] (epinephrine)
- Epi-Pen 0.3mg (epinephrine)
- Epi-Pen Jr. 0.15mg (epinephrine)

- **Manufacturer withdrew from the CMS rebate program in 2017*

Epinephrine, Self-Injected

- Self-injected epinephrines are indicated for the emergency treatment of Type I allergic reactions including anaphylaxis to stinging insects, biting insects, allergen immunotherapy, foods, drugs, diagnostic testing substances, and other allergens
- These products are also indicated for the emergency treatment of idiopathic anaphylaxis and exercise-induced anaphylaxis
- Patients should carry two doses of epinephrine. More than two sequential doses of epinephrine should only be administered under direct medical supervision
- Practice guidelines do not distinguish preference of one self-injectable epinephrine product over another

Epinephrine, Self-Injected

Product/Guideline Updates:

- American Academy of Pediatrics (AAP) updated their 2007 guidance on the use of epinephrine for anaphylaxis
- At-risk patients should be prescribed an epinephrine auto-injector for first line treatment of anaphylaxis, particularly if they have asthma
- AAP recommends against antihistamines for first line treatment of anaphylaxis

Epinephrine, Self-Injected

Product/Guideline Updates:

- In June 2017 Symjepi (epinephrine) was approved as a 0.3mg/0.3mL prefilled single-dose syringe for manual injection, indicated for the emergency treatment anaphylaxis and intended for patients at least 30 kg in weight
- Injected intramuscularly or subcutaneously into the anterolateral aspect of the thigh
- Contraindications, warnings, precautions and adverse reactions are similar to other epinephrine products
- There are no comparative data available
- Launch is anticipated in the second half of 2017

Antibiotics, Inhaled

Antibiotics, Inhaled

Class Overview: Products

- Bethkis (tobramycin)
- Cayston (aztreonam)
- Kitabis Pak (tobramycin)
- Tobi (tobramycin)
- Tobi Podhaler (tobramycin)
- tobramycin pak (tobramycin)
- tobramycin solution (tobramycin)

Antibiotics, Inhaled

- Inhaled antibiotics are used in the treatment of Cystic Fibrosis, autosomal recessive disorder
- As pulmonary infection is the main source of morbidity and mortality, antibiotics play an important role in CF therapy to control the progression of the disease
- The CF Foundation guidelines include both nebulized tobramycin and aztreonam as recommended therapy for the prevention and eradication of *Pseudomonas aeruginosa,* with a preference for tobramycin therapy for 28 days

Antibiotics, Inhaled

The Cystic Fibrosis Foundation also recommends:

- The CF Foundation also recommends alternate-month administration of both tobramycin and aztreonam in patients persistently infected with *P. aeruginosa*
- This is a grade B recommendation meaning there is a high certainty that net benefit is moderate or moderate certainty that net benefit is substantial
- The recommendation is based on a single published randomized, controlled trial of cycled therapy with aztreonam/tobramycin from 2008
- Patients (n=211) received one cycle of aztreonam after one cycle of tobramycin and were monitored for only 56 days to determine need for additional antibiotic therapy (IV or inhaled)

Antibiotics, Inhaled

Product/Guideline Updates:

- There is no recent clinical information or product specific news of significance for this class

Progestational Agents

Progestational Agents

Agents in Class

- Makena MDV (hydroxyprogesterone)
- Makena SDV (hydroxyprogesterone)

Progestational Agents

- Indicated to reduce the risk of preterm birth, defined as birth of an infant prior to 37 week of gestation, in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth
- Preterm birth, annually affects nearly 1 of every 9 infants born in the U.S. (*CDC – July 2016*)
- Not intended for use in women with multiple gestations or other risk factors for preterm birth
- Various hydroxprogesterone caproate formulations are not therapeutically equivalent
- Makena is available as multidose vial: 5 mL (250 mg/mL) and preservative free single-dose vial: 1 mL (250 mg/mL)

Progestational Agents

Product/Guideline Updates:

- There is no recent clinical information or product specific news of significance for this class

New Products (to Magellan PDL classes)

Richard L. Pope, R.Ph., Pharm.D.

AirDuo Respiclick (fluticasone proprionate & salmeterol)

- A fixed dose combination of a corticosteroid (fluticasone) and a LABA (salmeterol) indicated for the treatment of asthma in patients aged 12 years and older
- AirDuo is not indicated for the relief of acute bronchospasm
- Similar to other LABA containing products, AirDuo carries a black box warning of increased risks of asthma-related death along with increased risk of hospitalization in adolescents and pediatric patients
- AirDuo is contraindicated in *status asthmaticus*
- Do not use with a spacer or holding chamber

AirDuo Respiclick (fluticasone proprionate & salmeterol)

- Warnings include possible immunosuppression, increased risk of infections, impairment of adrenal function, hypercorticism and adrenal suppression similar to issues seen with other inhaled corticosteroid/LABA combinations
- Common adverse reactions include nasopharyngitis, oral candidiasis, back pain, headache and cough
- Due to possible drug interactions, use is not recommended with strong CYP3A4 inhibitors, MAOIs, tricyclic antidepressants, systemic beta-blockers and non-potassium sparing diuretics
- There are no randomized clinical studies of AirDuo or its individual components in pregnant women
- Patients with hepatic impairment should be monitored for systemic corticosteroid effects

AirDuo Respiclick (fluticasone proprionate & salmeterol)

- Starting dosage should consider prior asthma therapy and disease severity and is administered as one inhalation every 12 hours
- Safety and efficacy was evaluated in two confirmatory trials of 12 weeks duration, a 26 week safety trial and three dose-ranging trials with 3,004 patients with asthma. The efficacy of AirDuo Respiclick is based primarily on the dose-ranging trials and the confirmatory trials
- Efficacy results were similar in all trials with patients receiving AirDuo demonstrating significantly greater improvements in trough FEV1 from baseline scores
- AirDuo Respiclick is supplied in the following three strengths as a white dry-powder inhaler: 55mg/14mg, 113mg/14mg and 232mg/14mg

Bevyxxa (betrixaban)

- Bevyxxa is an oral factor Xa inhibitor indicated for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE
- The safety and efficacy of Bevyxxa has not been established in patients with prosthetic heart valves
- Bevyxxa is contraindicated in patients with an active pathological bleed
- Bevyxxa carries a boxed warning regarding the risk of spinal or epidural hematoma in patients who are taking the drug and who will receive neuraxial anesthesia or undergo spinal puncture
- Bevyxxa increases the risk of bleeding and can cause serious, potentially fatal bleeding when used concomitantly with drugs that affect hemostasis

Bevyxxa (betrixaban)

- Patients with severe renal impairment taking Bevyxxa may have an increased risk of bleeding and receive a reduced dose
- Concomitant use of P-gp inhibitors including, amiodarone, azithromycin, verapamil, ketoconazole, and clarithromycin lead to an increased exposure of betrixaban, and a dosage reduction should be considered
- The most common adverse reactions reported (≥ 2%) were urinary tract infection, constipation, hypokalemia, diarrhea, epistaxis, headache, hematuria, hypertension, and nausea
- The occurrence of major bleeding events included gastrointestinal, intracranial hemorrhage and any fatal bleed
- There is no data with the use of Bevyxxa in pregnant women and should only be used if the benefit outweighs the risk

Bevyxxa (betrixaban)

- Safety and effectiveness in pediatric patients have not been established
- The recommended dose of Bevyxxa is an initial single dose of 160 mg, followed by 80 mg once daily with food at the same time of day
- The recommended duration of treatment is 35 to 42 days
- At present, there is no reversal agent available
- APEX was a randomized, double-blind, double-dummy, active-controlled, multinational study comparing extended duration Bevyxxa to short duration of enoxaparin in the prevention of VTE in acutely medically ill hospitalized population with VTE risk factors
- The trial excluded patients whose condition required prolonged anticoagulation

Bevyxxa (betrixaban)

- A total of 7,513 patients were randomized 1:1 to either the Bevyxxa arm (160 mg orally on Day 1, then 80 mg once daily for 35 to 42 days AND enoxaparin subcutaneous placebo once daily for 6 to 14 days) or the enoxaparin arm (enoxaparin 40 mg subcutaneously once daily for 6 or 14 days AND Bevyxxa placebo orally once daily for 35 to 42 days)
- The primary efficacy endpoint was the composite of the occurrence of any of the following events including: asymptomatic proximal deep vein thrombosis (DVT) between days 32 through 47 (detected by ultrasound), symptomatic proximal or distal DVT, symptomatic non-fatal pulmonary embolism (PE), or VTE-related death from day 1 through day 42
- The primary safety outcome was major bleeding

Bevyxxa (betrixaban)

- The primary efficacy outcome rate was significantly improved in patients receiving the 80 mg dose of Bevyxxa versus enoxaparin across all cohorts, however the primary efficacy outcome rate was not significantly improved in patients receiving the 40 mg dose of Bevyxxa compared to enoxaparin across the cohorts
- Regarding the primary safety outcome, the rate of major bleeding events was not statistically different between the 80 mg dose of Bevyxxa versus enoxaparin, however, when combined with clinically relevant non-major bleeding, the rate was higher in the Bevyxxa group

Executive Session

Biosimilar Update

Suzi Berman, RPh

BIOSIMILAR UPDATE

- Enbrel
  - Erelzi (Etanercept-szzs) - Sandoz
- Humira
  - Amjevita (Adalimumab-atto) - Amgen
- Remicade
  - Renflexis (Infliximab-abda) - Pfizer
  - Inflectra (infliximab-dyyb) – Biogen

BIOSIMILARS

- Per AHCCCS Policy 310-V: AHCCCS Contractors shall not transition to a biosimilar drug until AHCCCS has determined that the biosimilar drug is overall more cost-effective to the state than the continued use of the brand name drug.

BIOSIMILARS

Coverage Determinations Per AHCCCS Policy 310-V

Preferred	Non-Preferred
Enbrel	Erelzi
Humira	Amjevita
Renflexis	Remicade
Inflexis	

New Drug Reviews

Suzi Berman, RPh

Four New Products

- Haegarda - C1 Esterase Inhibitor [Human]
- Baxdela – defloxacin
- Trulance - plecanatide
- Tymlos - abaloparatide

Haegarda - C1 Esterase Inhibitor Subcutaneous [Human]

- Indicated for routine prophylaxis of Hereditary Angioedema for adolescents and adults.
- Plasma derived concentrate of C1 Esterase Inhibitor
- Dosage: 60 units/Kg of body weight twice weekly subcutaneously.
- Black Box Warnings: None

Haegarda - C1 Esterase Inhibitor Subcutaneous [Human]

- Adverse Reactions occurring in more than 4% of subjects treated were:
  - Injection site reaction,
  - Hypersensitivity,
  - Nasopharyngitis and
  - Dizziness
- Clinical Trials – Double-blind, placebo controlled, cross-over study trials.

Haegarda - C1 Esterase Inhibitor Subcutaneous [Human] Clinical Trials cont'd

- 90 adult and adolescent subjects
  - Median age of was 40 years;
  - 60 participants were female and 30 were male.
  - Participants were randomized to receive either 60 IU/kg or 40 IU/kg Haegarda in one 16-week treatment period and placebo in the other 16-week treatment period.
  - Efficacy was evaluated for the last 14 weeks of each treatment period.

Haegarda - C1 Esterase Inhibitor Subcutaneous [Human] Clinical Trials cont'd

- Results were based on the reduction of HAE attacks when comparing Haegarda to placebo.
- The number of attacks for participants dosed at 60 IU/kg was 0.52 attacks per month as compared to 4.03 attacks if receiving placebo, a 89% reduction.

Haegarda - C1 Esterase Inhibitor Subcutaneous [Human] Clinical Trials cont'd

- The number of attacks for participants dosed at 40 IU/kg was 1.19 attacks per month as compared to 3.61 attacks for those receiving placebo, a 75% reduction.
- Recommendation is to not add Haegarda to the AHCCCS Drug List at this time and review this class of drugs at a future meeting because there are several other available products to treat HAE and they currently require prior authorization.
- Haegarda is available through the prior authorization process
- Vote

Baxdela - Delafloxacin

- A fluoroquinolone indicated for skin and skin structure infections caused by Methcillin Resistant Staph Aureus (MRSA) and Methcillin Susceptible Staph Aureus (MSSA) and various streptococcus, E. coli, Pseudomonas, Enterobacter and Klebsiella.
- Dosage: 450mg every 12 hours for 5-14 days.
  - Caution with the elderly and renal impaired patients
  - IV dosage equally converts to oral dosage
- Adverse Reactions
  - Nausea (8%), Diarrhea (8%), Headache (3%)
  - Transaminase elevations (3%), and Vomiting (2%)

Baxdela - Delafloxacin

- Black Box Warnings:
  - Serious adverse reactions that may be irreversible including:
    - Tendonitis and tendon rupture
    - Peripheral neuropathy
    - Central nervous system effects
    - Exacerbation of myasthenia gravis muscle weakness.
- Clostridium difficile associated diarrhea.

Baxdela - Delafloxacin

- Clinical Trials –
- 1510 adults with acute bacterial skin and skin structure infections were randomized at several sites, double-blind, comparator, non inferiority trials.
- Head to head study with the combination of Vancomycin + Azotreonam.

Baxdela – Delafloxacin Clinical Trials Cont'd

- Results: Baxdela was non-inferior to the drug combination of Vancomycin/Azotreonam.
- Recommendation is to not list Baxdela on the AHCCCS Drug List and to continue providing the drug through the prior authorization process due to the seriousness of the infections that the drug is being used for and the very serious potentially irreversible side effects.
- Vote

Trulance - Placanatide

- Indicated for chronic idiopathic constipation.
- Dosage: 3mg once daily
- Black Box Warning – Contraindicated for pediatric patients because it may cause dehydration.
- Recommendation is to not add Trulance to the AHCCCS Drug Lists because there are many products available that are more cost effective to the State for the treatment of constipation. Trulance is available through prior authorization.
- Vote

Tymlos – Abaloparatide

- Indicated for the treatment of osteoporosis.
- Dosage: 80mcg subcutaneously daily
- Black Box Warning:
  - Increased incidence of osteosarcoma
  - Treatment is not recommended for greater than 2 years
- Adverse Reactions – most common
  - Increased uric acid and urine calcium
  - Dizziness, nausea, headache, palpitations, fatigue
  - Upper abdominal pain, vertigo, injection site swelling.
  - Antibody development (no clinical significance)

Tymlos – Abaloparatide

- Clinical Trial – 18-month, randomized, multicenter, double-blind, placebo-controlled trial in postmenopausal women with a mean age of 69 years.
- Participants were given 80mcg of Tymlos or placebo.
- Results were measured as the incidence of new vertebral fractures in patients treated with Tymlos vs. Placebo.

Tymlos – Abaloparatide

- Results:
  - At 18 months - the incidence of participant vertebral fractures was much less for those given Tymlos (0.6%) versus that of Placebo (4.2%).
  - At 25 months - the incidence of participant vertebral fractures was much less for those given Tymlos (0.6%) versus that of Placebo (4.4%).

Tymlos – Abaloparatide

- Recommendation is to not add Tymlos to the AHCCCS Drug Lists at this time and to review the medication as part of the osteoporotic market basket at a future meeting.
- Tymlos is available through prior authorization.
- Vote

Agenda Items For The Next Meeting Thursday 12 October 2017

Please send agenda items to:

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Thank You.